Effect of Incretin Analogues and Dipeptidyl-peptidase-IV inhibitors on the risk of thyroid cancer

First published: 18/10/2023

Last updated: 27/03/2024

Study Finalised

Administrative details

EU PAS number

EUPAS107225

Study ID

107225

DARWIN EU® study

No

Study countries

☐ United States

Study description

Incretin based therapies are commonly used as second-line antihyperglycemic drugs in the treatment of type 2 diabetes mellitus. They promote glucose dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety or potentiate the action of incretin hormones by blocking DPP-IV – the enzyme responsible for the degradation of incretin hormones. Activation of the GLP-1 receptor has been shown to cause thyroid C-cell hyperplasia and C-cell tumors in carcinogenicity studies in preclinical studies using rodents prompting the U.S. Food and Drug Administration (FDA) to issue a warning regarding medullary thyroid cancer for long-acting GLP-1RA. Still, the relevance of these findings in humans is questionable, as there is a discrepancy in the level of expression and biology of GLP-1 receptors in the thyroid between rodents and primates. Currently, there remains uncertainty about the risk of thyroid cancer associated with the use of incretin (GLP-1)-based therapies with data from clinical and observational studies showing conflicting results. Some studies have reported no increased risk of thyroid cancer with the use of GLP-1RA relative to placebo or other antihyperglycemic drugs, while a recent study found an increased risk of all thyroid cancer and medullary thyroid cancer, particularly after 1-3 years of treatment. Most of the existing studies suffer from methodological issues, including short durations of follow-up, limited lag period, uncertainty about valid ascertainment of outcomes, diagnostic suspicion, insufficient confounding control, incomplete covariate ascertainment and inadequate power. Additionally, most studies so far have only focused on the effect of exenatide and liraglutide on thyroid cancer. This work, therefore, aims to address these issues, and contribute critical evidence to inform clinical decision-making by exploring the effect of GLP-1RA and DPP-IV inhibitors on thyroid cancer incidence.

Study status

Finalised

Research institutions and networks

Institutions

University of North Carolina at Chapel Hill

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Til Stürmer

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 29/06/2022

Actual: 29/06/2022

Study start date

Planned: 29/06/2022

Actual: 29/06/2022

Date of final study report

Planned: 31/12/2024

Actual: 17/10/2023

Sources of funding

- Other

More details on funding

National Institute on Aging at NIH

Study protocol

Effect of Incretin Analogs on risk of thyroid cancer.pdf(276.24 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Data collection methods:

Secondary use of data

Main study objective:

To estimate the comparative effect of GLP-1RA and DPP-IV inhibitors versus sodium-glucose cotransporter-2 (SGLT-2) inhibitors on the incidence of thyroid cancer.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(A10AE) Insulins and analogues for injection, long-acting

Insulins and analogues for injection, long-acting

(A10BH) Dipeptidyl peptidase 4 (DPP-4) inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors

(A10BJ) Glucagon-like peptide-1 (GLP-1) analogues

Glucagon-like peptide-1 (GLP-1) analogues

(A10BK) Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Medical condition to be studied

Type 2 diabetes mellitus

Population studied

Short description of the study population

The study population involved patients aged 66 years or older, prescribed with GLP-1RA, DPP-IV inhibitors or SGLT-2 inhibitors between January 1, 2008, and December 31, 2018 identified from the Medicare Fee-for-Service Database.

Age groups

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

Special population of interest

Frail population

Estimated number of subjects

100000

Study design details

Outcomes

The primary outcome is thyroid cancer (TC).

Data analysis plan

The main effect measure estimate will be standardized incidence rate differences (IRD) with the assumption that there is no unmeasured confounding. We will also estimate IRD within different times after antihyperglycemic drug initiation to allow for incidence rates to vary over time. Secondary effect measure will be hazard ratios. When estimating risks of cancer outcomes in older Medicare patients, censoring those who died prior to having the outcome of interest, as commonly done in survival analyses, could introduce bias in the risk estimation. To avoid this, we will employ Aalen Johansen (AJ) estimators to estimate risks.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Medicare Fee-for-Service (FFS) Database

Data sources (types)

Administrative healthcare records (e.g., claims)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No